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The race for clinical trials on Omicron-based COVID-19 vaccine candidates: Updates from global databases

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Abstract

The coronavirus disease 2019 (COVID-19) has caused more than 6.5 million deaths globally as of June 10, 2022. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant (B.1.1.529) has the greatest transmission rate and can cause hospitalization in vaccinated individuals. It has been the most distinct SARS-CoV-2 variant of concern to date. The existing inactivated vaccines made with the wild-type strain are less efficient to prevent disease and/or hospitalization associated with the Omicron variant, even after a booster dose. Hence, it is crucial to develop new vaccines that are effective against this variant. The objective of this study was to summarize the data on existing clinical trials for new COVID-19 vaccines formulated against Omicron variant. Clinical trials from the international clinical trials registry platforms were searched and analyzed. As of June 10, 2022, a total of 15 clinical trials are available consisting of six and nine clinical trials of inactivated and messenger RNA (mRNA)-based vaccine candidates containing the Omicron variant, respectively. Those trials are evaluating four inactivated and four mRNA-based vaccine candidates. Although Omicron-specific vaccines are highly desired, their development is challenging since the SARS-CoV-2 variant formation is still unpredictable. Although two vaccines from Pfizer and Moderna have been approved for emergency use in the US and the UK for Omicron variant, the Asian pharmaceutical companies such as CNBG (Sinopharm), Sinovac, and Shifa Pharmed also have Phase 3 clinical trials under development and almost all clinical trials are expected to be completed in 2023. These results should help guide academics and policymakers in the COVID-19 vaccine field regarding investments in updated booster doses against the SARS-CoV-2 Omicron variant.

Keywords: COVID-19, vaccine, SARS-CoV-2, Omicron variant, clinical trial

Introduction

As of June 2022, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused approximately 6.3 million deaths globally [1]. The surge of the SARS-CoV-2 Omicron variant (B.1.1.529) in 2021 raised concerns about the effectiveness of the current COVID-19 vaccines against the Omicron variant and its sub-lineages BA.1, BA.2, and BA.3. The Omicron variant, which has 37 mutations in the spike (S) glycoprotein [2] and greater transmission ability, is capable of causing disease and hospitalization in vaccinated individuals [3, 4]. Hence, the Omicron variant is the most evolutionarily distinct

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SARS-CoV-2 variant of concern to date [5], more than Delta and the other main variants such as Alpha, Beta, and Gamma. In addition, some monoclonal antibodies (mAbs), such as etesevimab and bamlanivimab, are unable to neutralize the Omicron variant [6].

Non-prophylactic antiviral treatments for COVID-19 have been approved for emergency use such as remdesivir, molnupiravir, and the nirmatrelvir-ritonavir combination. Although remdesivir is a COVID-19 treatment to reduce hospitalization days and adverse events, recent evidence indicates that it is not strongly associated with an improvement in the need for mechanical ventilation and reduced mortality [7, 8]. Although some antivirals have shown potent activity in vitro against the Omicron variant and Paxlovid was associated with a reduction in viral load, disease progression, all-cause mortality, and risk of invasive mechanical ventilation [9, 10], the variant has been associated with the recurrence of COVID-19 symptoms along with testing positive again, even after having tested negative [11,12].

After the appearance of the Omicron variant, the use of vaccine booster doses was strongly recommended to reduce the risk of hospitalization and death [13]. A study assessing the blood samples from individuals who were double- or triple-vaccinated with the messenger RNA (mRNA)-based COVID-19 vaccine from Pfizer and BioNTech (BNT162b2) found that vaccination induced neutralization of Omicron BA.1, BA.2, and previous SARS-CoV-2 variants, but not against the newest sub-lineages BA.4 and BA.5 [5]. Another study found that two-dose of from Sinopharm inactivated vaccine was inadequate to provide full protection against these newly emerging variants and a third booster dose only exhibited 75% of neutralizing activity against the sub-lineages BA.1, BA.1.1, BA.2, and BA.3 [14].

Those data demonstrate that finding effective vaccines for emerging variants of SARS-CoV-2 in particular Omicron is critical in saving lives and minimizing hospital admission [12]. The aim of this study to summarize and analyze the data on the existing clinical trials of new COVID-19 vaccine candidates formulated with the Omicron variant including the characteristic features of vaccine candidates.

Methods

An observational study with qualitative approach based on database records was conducted. To identify relevant clinical trials regarding vaccine candidates formulated with the Omicron variant, searches on the Clinicaltrials.gov database and the International Clinical Trials Registry Platform (ICTRP) search portal were conducted. Clinicaltrials.gov is a resource from the U.S. National Library of Medicine containing clinical studies conducted in 209 countries. The ICTRP from the World Health Organization (WHO) provides a central database with trial registrations from several countries.

We performed the searches on June 10, 2022 using the advanced search feature at clinicaltrials.gov, with the keywords: [COVID-19] in the "Condition or disease" field and [vaccine AND Omicron] in the "Other words" field. We selected only [Interventional Studies] in the "Study type" field. In the ICTRP search portal, we used the advanced search with the keyword [Omicron] in the "Title" or "Intervention" fields, the [COVID-19] as a keyword in "Condition", using the "recruitment status" (ALL), and clicking on "Restrict to COVID-19." We retrieved the documents and analyzed them manually to eliminate duplicates. We analyzed the collected documents based on their titles, sponsors, and the National Clinical Trial (NCT) numbers.

Results

We retrieved 42 clinical trials from the Clinicaltrials.gov database and six trials from the ICTRP portal. After sorting, we identified 15 clinical trials reporting the use of inactivated or mRNA vaccines against SARS-CoV-2 Omicron variant (**Table 1**). Chinese companies have the largest number of clinical trials, followed by US sponsors.

The Moderna (US) vaccine against the Omicron variant (mRNA-1273.529) has the most clinical trials with five trials. The Shifa Pharmed Industrial Group (Iran), Sinovac (China), Pfizer (US)/BioNTech (Germany), the China National Biotec Group (CNBG, China), and Moderna (US) have each reported at least one Phase 3 clinical, while Chinese Wuhan Recogen Biotechnology

Company (WRBC) has reported only a Phase 1 trial for a lyophilized COVID-19 mRNA vaccine containing S glycoprotein of the Omicron variant.

The US governmental agency National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring one clinical trial with a vaccine from Pfizer/BioNTech with the Omicron variant (BNT16b2 Omi), comparing its safety and immunogenicity with other vaccines containing older SARS-CoV-2 variants, including B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta). The NIAID has played an important role in sponsoring and developing vaccines, including for Zika virus [15] and COVID-19 [16].

Inactivated vaccines with the SARS-CoV-2 Omicron variant

There are six clinical trials of inactivated vaccine candidates being conducted globally. Two of clinical trials on the same inactivated vaccine candidate are sponsored by Sinovac Biotech (China) NCT05411471 (Phase 2) and NCT05381350 (Phase 3) (**Table 1**). The inclusion criteria for volunteers in these trials include healthy adults aged 18-65 years who have received two or three doses of Comirnaty® (Pfizer/BioNTech) or CoronaVac®, with the last dose given at least 90 days before the day of a booster vaccination. As of June 10, 2022, both trials had the recruitment status as “not recruiting yet” and the estimated study completion date will be March 2023.

All clinical trials sponsored by the China National Biotech Group (CNBG) show the recruitment status as “recruiting.” The first one (NCT05365724) [17] aims to evaluate the safety and immunogenicity of a new Omicron COVID-19 inactivated vaccine in an unvaccinated population aged ≥ 18 years. The estimated study completion date is June 1, 2023. Another study (NCT05374954) [18] is being conducted with people who had been vaccinated with two or three doses of any COVID-19 vaccine. The participants were given the inactivated vaccine, manufactured by the Beijing Institute of Biological Products (BIBP) and the estimated study completion date is November 10, 2023. A third trial sponsored by the CNBG (NCT05382871) [19] is also in Phase 3 with adult participants ≥ 18 years who had been vaccinated with two or three doses of COVID-19 inactivated vaccine or mRNA vaccine. This study has three groups of participants: (1) COVID-19 inactivated vaccine (prototype variant), (2) BIBP-COVID-19 inactivated vaccine (Omicron), and (3) inactivated vaccine with the Omicron variant manufactured by the Wuhan Institute of Biological Products (WIBP). This clinical trial has an estimated completion date of November 27, 2023.

The last clinical trial retrieved with inactivated vaccines was one with an aluminum adjuvant formulated with an Omicron strain sponsored by the Iranian pharmaceutical company Shifa Pharmed Industrial Group (IRCT20171122037571N4). This Phase 3 non-randomized clinical trial [20] is being conducted in 210 volunteers aged ≥ 18 years, to evaluate the immunogenicity, safety, and adverse effects of the CovIran Barkat of Omicron Strain in individuals who had received two doses of inactivated vaccines for COVID-19 in comparison with the original Wuhan strain vaccine.

mRNA vaccines

There are nine clinical trials of mRNA vaccine candidates being conducted. Wuhan Recogen Biotechnology Company (WRBC) is testing a COVID-19 vaccine containing an mRNA sequence of S glycoprotein derived from the Omicron variant, formulated with specific lipid nanoparticles (LNP) [21]. It has been optimized with a lyophilization technique that better sustains physiochemical and bioactivity properties, achieving long-term storage at 2-8°C. It is in Phase 1 (NCT05366296) to evaluate the safety, reactogenicity, and immunogenicity of one booster dose in adults aged 18-60 years. It shows a recruitment status of “recruiting” and it is estimated to be completed by January 2023 [22].

Three vaccine candidates being evaluated in five different clinical trials are sponsored by Moderna (**Table 1**). The vaccines are made with the RNA sequences of S glycoprotein derived from the Omicron variant: the monovalent mRNA-1273.529, the bivalent mRNA-1273.214 that also contains the RNA sequences from the wild-type virus (mRNA-1273), and the actualized mRNA-1273.222 (with the Omicron BA.4/5 sub-lineages plus wild-type).

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Table 1. Clinical trials on COVID-19 vaccines using the Omicron variant retrieved from www.clinicaltrials.org and International Clinical Trials Registry Platform (ICTRP) as of 10 June 2022

Sponsor (Country)	Clinical trial title	Vaccine platform	Phase	NCT number (Number of participants)	Study design			Expected completion date
					Random	Blinding	Comparator group	
Sinovac Biotech (China)	A Phase 2b, randomized, open-labeled trial to evaluate the immunogenicity and safety of one or two doses of booster vaccine with the COVID-19 vaccine (Vero cell), inactivated, Omicron strain in adults in Hong Kong	Inactivated with Omicron strain	2	NCT05411471 (300)	Yes	None	CoronaVac®	8 March 2023
	A randomized, double-blind, active-controlled clinical trial, as well as an immuno-bridging clinical trial by parallel testing previous serum after primary immunization, to evaluate the immunogenicity and safety of booster immunization of COVID-19 vaccine (Vero cell), inactivated (Omicron variant) in healthy people aged 18 years and above	Inactivated, with Omicron strain	3	NCT05381350 (1750)	Yes	Double	Inactivated vaccine with a prototype strain	20 August 2023
China National Biotech Group (China)	A study to evaluate the safety and immunogenicity of Omicron COVID-19 vaccine (Vero cell), inactivated in population 18 years old of age and above with no vaccination history of COVID-19 vaccine	Inactivated SARS-CoV-2 Omicron variant	1/2	NCT05365724 (280)	No	None	None	1 June 2023
	Safety and immunogenicity study on Omicron inactivated COVID-19 vaccine and prototype inactivated COVID-19 vaccine in population aged 18 years old and above vaccinated the prototype inactivated COVID-19 vaccine	Inactivated SARS-CoV-2 Omicron variant	3	NCT05374954 (4200)	Yes	Quadruple	Inactivated vaccine with SARS-CoV-2 strain	10 November 2023
	Sequential immunization of two doses of inactivated COVID-19 vaccine (Omicron) in vaccinated population aged 18 years and above	Inactivated SARS-CoV-2 Omicron variant	3	NCT05382871 (1800)	Yes	Triple	mRNA vaccine	27 November 2023
Shifa Pharmed Ind. Group Co (Iran)	A clinical trial to evaluate the immunogenicity and safety of Omicron-Based CovIran Barkat vaccine as a third injection dose in vaccinated population over 18 years of age	Inactivated CovIran Barkat vaccine with an Omicron strain	3	IRCT20171122037571N4 (210)	No	No	CovIran Barkat vaccine with a Wuhan strain	N/A
Wuhan Recogen Biotechnology (China)	A randomized, observer-blinded, placebo-controlled Phase 1 study to evaluate the safety, reactogenicity, and immunogenicity of one dose booster by a lyophilized COVID-19 mRNA vaccine in adults aged 18 to 60 years	Lyophilized mRNA Omicron variant sequences from S glycoprotein	1	NCT05366296 (24)	Yes	Quadruple	Placebo (0.9% sodium chloride solution)	January 2023
Moderna Tx (US)	Phase 2, randomized, observer-blind, investigator-initiated, collaborative study to evaluate the safety and immunogenicity of omicron variant-matched vaccine booster in adults	mRNA-1273.214 (Omicron variant vaccine plus wild-type strain)	2	NCT05383560 (150)	Yes	Double	Placebo (0.9% sodium chloride solution)	June 2023

Sponsor (Country)	Clinical trial title	Vaccine platform	Phase	NCT number (Number of participants)	Study design			Expected completion date
					Random	Blinding	Comparator group	
	A Phase 2a, randomized, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2	mRNA-1273.529 – (Omicron variant vaccine)	2	NCT05137236 (543)	Yes	Quadruple	3 groups: mRNA 1273, mRNA-1283 and mRNA-1283.211 (Wuhan wild-type strain plus beta variant)	30 March 2023
	a Phase 2/3, randomized, observer-blind, active-controlled, multicenter study to evaluate the immunogenicity and safety of omicron variant vaccines in comparison with mRNA-1273 (prototype) booster vaccine	mRNA-1273.529 (Omicron strain) and mRNA-1273.214 (Omicron strain plus wild-type strain)	2/3	NCT05249829 (3924)	Yes	Quadruple	mRNA-1273	7 April 2023
	A Phase 2/3 study to evaluate the immunogenicity and safety of mRNA vaccine boosters for SARS-CoV-2 variants	mRNA-1273.529 and mRNA-1273.214 and mRNA-1273.222 (sub lineages BA.4/5 Omicron variant plus wild-type)	2/3	NCT04927065 (5058)	No	None	4 groups: mRNA-1283.211, mRNA-1273, mRNA-1273.617.2 (Delta variant) and mRNA-1283.213 (Beta + Delta variant)	30 April 2023
	A Phase 2/3, randomized, observer-blind, active-controlled, multicenter study to evaluate the immunogenicity and safety of mRNA-1273.529 (B.1.1.529, Omicron variant) in comparison with mRNA-1273 (prototype) booster vaccine	mRNA-1273.529	2/3	ISRCTN99890480 (2924)	Yes	Yes	mRNA 1273	17 March 2023
NIAID (US)	Phase 2 clinical trial to optimize immune coverage of SARS-CoV-2 existing and emerging variants	mRNA COVID-19 with sequences from S glycoprotein of Omicron variant - BNT162b2 Omi (B.1.1.529) (Pfizer/BioNTech)	½	NCT05289037 (1500)	Yes	None	10 groups: placebo, AS03 (oil-in-water emulsion) + CoV2 preSdTM/strains prototypa+Beta, AS03+ CoV2 preS dTM Beta strain, AS03+CoV2 preS dTM Prototype strain, BNT162b2 (Pfizer/BioNTech), BNT162b2 (Beta), mRNA-1273, mRNA-1273.351, and mRNA-1273.617.2	28 March 2026
BioNTech (Germany)/ Pfizer (US)	A Phase 2 trial to evaluate the safety and immunogenicity of SARS-CoV-2 monovalent and multivalent RNA-based vaccines in healthy subjects	mRNA BNT162b2 Omicron variant Omi (B.1.1.529) vaccine	2	NCT05004181 (1383)	No	None	5 groups: BNT162b2 (prototype), BNT162b2 (Beta+Delt), BNT162b2(Beta),	January 2024

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Sponsor (Country)	Clinical trial title	Vaccine platform	Phase	NCT number (Number of participants)	Study design			Expected completion date
					Random	Blinding	Comparator group	
							BNT162b2 (Delta), Observational	
	A Phase 3 master protocol to evaluate additional dose(s) of bnt162b2 in healthy individuals previously vaccinated with BNT162B2	BNT162b2 Omi (B.1.1.529) combination with BNT162b2 vaccine	3	NCT04955626 (16373)	Yes	Triple	4 groups: placebo, BNT162b2 (prototype), combination BNT162b2 (prototype) and BNT162b2 Omi (B.1.1.529), and bivalent BNT162b2 (prototype)/BNT162b2 Omi (B.1.1.529)	12 April 2023

B.1.1.529: Omicron variant; BIPB: Beijing Institute of Biological Products; mRNA: messenger ribonucleic acid; Omi: Omicron variant; S: SARS-CoV-2 spike glycoprotein; SARS-CoV-2: severe acute respiratory syndrome adverse coronavirus 2; US: United States of America; WIBP: Wuhan Institute of Biological Products

The most advanced randomized clinical trials (NCT05249829 and ISRCTN99890480) [23,24], both are Phase 2/3, evaluate the immunogenicity, safety, and reactogenicity of a single booster dose of mRNA vaccines. The participants are those have been vaccinated with two or three doses of any authorized/approved COVID-19 vaccine. In trial NCT05249829, the participants who had received two doses of a COVID-19 vaccine as a primary series will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the third dose [23]. Also, the participants who had received a primary series and one booster dose will receive mRNA-1273.529, mRNA-1273.214, or mRNA-1273 as the fourth dose. In the trial ISRCTN99890480, the participants being received mRNA-1273.529 in comparison with the mRNA-1273 as the third dose [24].

Another relevant clinical trial sponsored by Moderna, with 5058 participants, is the NCT04927065 [25]. This trial is evaluating the immunogenicity, safety, and reactogenicity of booster doses of mRNA-1273.529, mRNA-1273.214, and mRNA-1273.222. This last one product is formulated with two different SARS-CoV-2 variants, the sub lineages BA.4/5 Omicron plus the wild-type variant

There are two clinical trials sponsored by Pfizer/BioNTech and the most advanced study (Phase 3) vaccine is NCT04955626 [26]. It started in July 2021 and is already recruiting the participants, with an estimated primary completion date of September 13, 2023. This clinical trial is evaluating the safety, tolerability, and efficacy of the administration of a booster dose of BNT162b2-Omi to participants who had been vaccinated with two doses of Comirnaty® six months or more before randomization. The Comirnaty® vaccine contains a nucleoside-modified mRNA encoding the S glycoprotein of SARS-CoV-2 [27] and has been authorized in 146 countries [28]. In this clinical trial, more than 10,000 participants have been recruited: 5,081 received a third BNT162b2-Omi dose and 5,044 received a placebo.

Discussion

Currently, 40 SARS-CoV-2 vaccines generated from different platforms have been authorized or approved around the world. For example, the recombinant protein vaccine from Novavax (Nuvaxovid®) has been approved in 37 countries [28]. The recombinant viral vector vaccines, such as Covishield® from AstraZeneca/Oxford University and the one from Janssen Pharmaceuticals (Ad26.COV2.S), have been approved in more than 100 countries [28]. On the other hand, only inactivated and mRNA-based vaccines have advanced the development of Omicron variant clinical trials (**Table 1**).

It is important to note that the original BioNTech/Pfizer and Moderna mRNA vaccines were the most purchased from January to June 2021 and accounted for 70% of all COVID-19 vaccine and drugs sales with revenues of US$ 36 billion [29]. This revenue is expected to increase to US$ 39 billion in 2022 [29]. Given that these products are so profitable, developing a vaccine against the Omicron variant is an obvious path for these companies to pursue.

In this scenario, the WRBC must have also visualized future revenues and profits on investment in a lyophilized mRNA vaccine modified with the Omicron variant for COVID-19 prevention. Similarly, Sinovac sales have increased significantly since the approval of their CoronaVac® vaccine, with approximately US$ 11 billion in the first six months of 2021 [30]. However, compared with Comirnaty® this product does not induce enough protective antibodies against the Omicron variant even after a booster dose [31].

The CNBG, BIBP, and the WIBP are subsidiaries of the China National Pharmaceutical Group (Sinopharm), a state-owned pharmaceutical company. Sinopharm's vaccines also enhanced their revenues in 2021 [32]. These two vaccines showed a weaker performance with a booster dose for the Omicron variant [33]. These two factors have likely encouraged Sinovac and Sinopharm to work on developing effective vaccines against the Omicron variant.

Although these Omicron-specific vaccines are highly desired, their development is not as straight forward as the seasonal influenza vaccines, which are updated every year with the globally circulating variants. Since SARS-CoV-2 variant formation is still unpredictable [34], the Vaccines and Related Biological Products Advisory Committee (VRBPAC) have held the meeting and discussed the upcoming approaches to COVID-19 vaccine variant composition decision-making, development, and recommendations [35]. Other discussions have started between the VRBPAC

and the FDA for the annual development of COVID-19 vaccines similar to those produced for the influenza viruses [35].

Conclusions

The development of an Omicron variant COVID-19 vaccine has already started, mostly by Chinese and US sponsors, and with clinical trials expected to end by 2023. Even though the Pfizer and Moderna bivalent vaccines have already been approved for emergency use in the US and the UK, the Asian pharmaceutical companies CNBG (Sinopharm), Sinovac, and Shifa Pharmed also have Phase 3 clinical trials under development. Omicron-based vaccines are critical and its development need to be prioritized in order to control the ongoing COVID-19 pandemic.

Ethics approval

Not Applicable

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Conflict of interest

All the authors declare that there are no conflicts of interest.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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